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(54) Title: SOFT GELATIN CAPSULES HAVING IMPROVED STABILITY BY INCORPORATION OF EMBRITTLEMENT INHIBITING SUBSTANCES (57) Abstract A pharmaceutical dosage unit form comprises one or more pharmaceutically active materials dissolved or suspended in a liquid polyethylene glycol and encapsulated in a soft gelatin capsule shell, in which the capsule shell comprises gelatin, a plasticizer therefor, and an embrittlement inhibiting composition comprising a mixture of sorbitol and one or more sorbitans. Preferably the polyethylene glycol also contains glycerin, sorbitol or propylene glycol.		

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Soft Gelatin Capsules Having Improved Stability By
Incorporation of Embrittlement Inhibiting Substances

BACKGROUND OF THE INVENTION

Field of the Invention and
Description of the Prior Art

This invention is concerned with improvements in and relating to
5 pharmaceutical compositions and, more particularly, is concerned with
pharmaceutical compositions in dosage unit form encapsulated in soft
gelatin capsules.

Pharmaceutical compositions in dosage unit form encapsulated in
soft gelatin capsules (hereinafter simply referred to as "capsules") are
10 well known and basically consist of a "fill", comprising one or more
pharmaceutically active materials dissolved or dispersed in an appropriate
liquid vehicle, encapsulated in a soft gelatin shell, generally comprising
gelatin together with a plasticizer therefor such as glycerin.

On class of vehicle which has been proposed for use in the fill
15 comprises the liquid polyethylene glycols, for example polyethylene
glycols having a molecular weight from about 100 to 600. Certain
pharmaceutically active ingredients, for example benzodiazepine type
compounds such as temazepam and lormetazepam, have been shown to
have improved bioavailability when administered as polyethylene glycol
20 solutions in soft capsules.

However, the use of a liquid polyethylene glycol as a carrier vehicle
has an attendant disadvantage in that the material is hygroscopic and
tends to absorb water from the shell and thereby embrittle it. This
embrittlement may be enhanced by migration of the plasticizer from the
25 shell into the fill. As a result of such embrittlement, which may take
place over a matter of months or years, the shell loses its elasticity and,
hence, its resistance to mechanical shocks which are, encountered in
handling and transport of the capsules. In extreme cases the capsules may
be sufficiently embrittled and/or suffer such mechanical shocks that a
30 capsule is ruptured.

The problem is not so severe as to render capsules having a fill
comprising a liquid polyethylene glycol vehicle useless. Many thousands,
or indeed millions, of such capsules survive transport and handling without
breakage. However, the problem does exist and is exacerbated by the
35 fact that, since capsules are commonly packed together in several tens,



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hundreds or even thousands, one breaking, and therefore leaking, capsule can damage other capsules in the same package and thus render a large number of capsules useless.



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SUMMARY OF THE INVENTION

It has now been found, in accordance with the present invention, that the problem of embrittlement may be reduced by incorporating in the shell sorbitol in admixture with one or more sorbitans and, possibly, other
5 polyols, and at the same time incorporating glycerin, sorbitol or propylene glycol in the liquid polyethylene glycol vehicle of the fill of the capsules.



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DETAILED DESCRIPTION OF THE
PREFERRED EMBODIMENT

Accordingly, the invention provides a pharmaceutical dosage unit form comprising one or more pharmaceutically active materials dissolved
5 or suspended in a liquid polyethylene glycol and encapsulated in a soft gelatin capsule shell, in which the capsule shell comprises gelatin, a plasticizer therefor and an embrittlement inhibiting composition comprising a mixture of sorbitol and one or more sorbitans.

Typically, the embrittlement inhibiting composition comprises from
10 25 to 45% by weight of sorbitol and from 20 to 30% by weight of sorbitans (the major proportion of the sorbitan component being 1,4-sorbitan) together with water (typically in an amount of 13 to 20% by weight) and other polyhydric alcohols, the mannitol content being from 0 to 6% by weight.

15 Preferably the polyethylene glycol also contains glycerin, sorbitol or propylene glycol. In this case, the amount of glycerin, sorbitol or propylene glycol dissolved in the liquid polyethylene-glycol fill is suitably from 1 to 20% by weight, preferably from 2 to 12% by weight, more preferably from 3 to 8% by weight.

20 The amount of sorbitol/sorbitan(s) mixture in the shell is suitably from 4 to 25% by weight, preferably from 6 to 20% by weight, more preferably from 9 to 15% by weight.

As noted above, the sorbitol/sorbitan(s) mixture may contain other polyhydric alcohols but in this case the total amount of sorbitol and
25 sorbitan(s) in the whole sorbitol/sorbitan(s)/other polyhydric alcohol(s) mixture is suitably from 45 to 75% by weight, preferably from 55 to 68% by weight. The other polyhydric alcohols are suitably hydrogenated saccharides.

The total mixture suitably contains not more than 6% by weight of
30 mannitol and preferably contains from 1 to 4% by weight, more preferably from 2 to 3% by weight of mannitol.

Suitable materials for introducing the sorbitol/sorbitan(s)/polyhydric alcohol(s) mixture into the capsule shell are concentrated aqueous solutions of polyhydric alcohols derived from the hydrolysis and partial
35 hydrogenation of glucose syrup. An example of a suitable commercially



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available material is that sold under the Trade name "Anidrisorb 35/70".

This product has the typical analysis listed below:

Components (% by weight of concentrated aqueous solutions):

	<u>D Sorbitol</u>	<u>Sorbitans</u>	<u>Other polyols</u>	<u>Mannitol</u>	<u>Water</u>
5	25-46%	20-30%	20-25%	0-6%	13-20%

In addition to the sorbitol/sorbitan(s) mixture, the gelatin material of the capsule shell will also contain a plasticizer, such as glycerin, propylene glycol or sorbitol (in addition the sorbitol in the sorbitol/sorbitane mixture), and this is suitably present in an amount of
 10 from 10 to 40% by weight, preferably from 25 to 45% by weight. Further the shell material may contain other conventional ingredients such as coloring agents (pigments or dyestuffs), and oxidant or preservative materials such as potassium sorbate and ethyl, methyl and propyl parabens.

15 The pharmaceutically active component of the compositions of the invention may be any of a wide variety of orally administrable pharmaceutical materials. Where the material is insufficiently soluble in the liquid polyethylene glycol vehicle, the fill may contain co-solvents, such as water or ethanol, or suspending or dispersing agents. Preferably,
 20 however, the pharmaceutical material is one soluble in the liquid polyethylene glycol vehicle such as the benzodiazepines type compounds mentioned above.

In order that the invention may be well understood the following examples are given by way of illustration only.

25 Soft gelatin capsules were produced having the fill composition and shell composition noted below.

Example 1

Temazepam Capsules, 10 mg

(a) Fill composition in mg per capsule

30	Temazepam	10 mg
	Polyethylene glycol 400	230 mg
	Glycerin	13 mg



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(b) Dry Shell Composition (% by weight)

	Gelatin	52%
	Glycerin	32%
	Anidrisorb 35/70	12%
5	Water	5%

Example 2Temazepam Capsules, 20 mg(a) Fill Composition in mg per capsule

	Temazepam	20 mg
10	Polyethylene glycol	460 mg
	Glycerin	26 mg

(b) Dry Shell Composition

	Gelatin	51%
	Glycerin	32%
15	Anidrisorb 35/70	12%
	Water	5%

Example 3Lormetazepam Capsules, 0.5 mg(a) Fill Composition in mg per capsule

20	Lormetazepam	0.5 mg
	Polyethylene glycol	115 mg
	Glycerin	6.5 mg

(b) Dry Shell Composition

	Gelatin	51%
25	Glycerin	32%
	Anidrisorb 35/70	12%
	Water	5%

Example 4Lormetazepam Capsules, 1 mg30 (a) Fill Composition in mg per capsule

	Lormetazepam	1 mg
	Polyethylene glycol	230 mg
	Glycerin	13 mg



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(b) Dry Shell Composition % by weight

	Gelatin	51%
	Glycerin	32%
	Anidrisorb 35/70	12%
5	Water	5%

Examples 5 and 6

Soft elastic gelatin capsules were produced from a fluid gelatin composition comprising (in % by weight):

	Gelatin	38.5%
10	Glycerol	20.7%
	Anidrisorb 35/70	8.8%
	Water	32.0%

filled with a liquid fill comprising (in % by weight):

	Temazepam	3.92%
15	Polyethylene glycol 400	96.08%

Two batches of capsules were produced, the first (Example 5) containing 10 mg of Temazepam per capsule and the second (Example 6) containing 20 mg of Temazepam per capsule.

By way of comparison, gelatin capsules were produced using the same fill but using a conventional shell forming composition comprising (in % by weight):

	Gelatin	42.06%
	Glycerol	24.30%
	Water	33.64%

Again two batches of capsules were produced, the first (Comparative Example 1) containing 10 mg of Temazepam per capsule and the second (Comparative Example 2) containing 20 mg of Temazepam per capsule.

The batches of capsules were stored at 20° C for several months and the hardness of samples of the batches was tested at intervals using a Harais-Hardness tester. Basically, this instrument operates by compressing the capsule under test for 20 seconds between a plunger attached to a load cell and a platform which is automatically raised. Thus, in order to test a capsule, it is placed horizontally on the platform so that it is in contact with both the platform and the plunger. During the



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test, the platform rises automatically and the load cell indicator displays the value of the resistance of the capsule to the compressive force. After 20 seconds the test is completed and the value displayed represents the hardness of the capsule under test.

- 5 In practice it has been found, as a matter of experience, that a hardness of greater than 12 Newtons, measured as described above, indicates that breakage through embrittlement of the capsule may be expected as a particular problem.

The results of the tests are shown in Table 1.

10

Table 1

Hardness (Newtons) stored at 20°C for

Example	0 month	1.7 months	6.7 months	7.8 months	9.8 months
6	8.0	9.8	11.5	12.16	12.3
15 6	5.25	8.0	10.4	11.2	11.9
Comp. 1	9.95	11.65	13.75	13.65	13.75
Comp. 2	7.3	10.6	12.75	13.25	13.2

- It may be seen from these results that the capsules in accordance with the invention have generally lower initial hardnesses than comparable corrected capsules and that they have effective storage lives, considered as lives during which their hardness is 12 or less, at least twice as long as those of the comparable conventional capsules.
- 20

Examples 7 and 8

- Soft elastic gelatin capsules were produced from a fluid gelatin composition comprising (in % by weight):
- 25

Gelatin	40.67%
Glycerol	18.02%
Anidrisorb 35/70	7.53%
Water	33.58%

- 30 filled with a fill comprising (in % by weight):

Temazepam	3.92%
Glycerol	5.0%
Water	0.38%
Polyethylene glycol 400	90.2%



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Two batches of capsules were prepared, one (Example 7) containing 10 mg of Temezepam per capsule and the other (Example 8) containing 20 mg of temazepam per capsule.

The batches were divided into three lots and each lot was stored at a temperature of 20°C, 30°C, and 40°C, respectively. The hardness of the capsules were determined as described in Examples 5 and 6 to give the results shown in Table 2.

Table 2

Hardness (Newtons) stored for				
10	Example (storage temperature - °C)	0 month	1 month	3.5 months
	7(20)	7.93	-	10.60
	7(30)	7.93	-	11.32
	7(40)	7.92	11.34	10.43
15	8(20)	6.91	-	10.22
	8(30)	6.91	-	11.23
	8(40)	6.91	10.20	11.05



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CLAIMS

1. A pharmaceutical dosage unit form comprising one or more pharmaceutically active materials dissolved or suspended in a liquid polyethylene glycol and encapsulated in a soft gelatin capsule shell, in which the capsule shell comprises gelatin, a plasticizer therefor and an embrittlement inhibiting composition comprising a mixture of sorbitol and one or more sorbitans.
2. A dosage unit form as claimed in claim 1 in which the embrittlement inhibiting composition comprises from 25 to 45% by weight of sorbitol and from 20 to 30% by weight of sorbitans together with water and other polyhydric alcohols.
3. A dosage unit form as claimed in claim 2, in which the embrittlement inhibiting composition contains not more than 6% by weight of mannitol.
4. A dosage unit form as claimed in claim 1 in which the shell contains from 4 to 25% by weight of the sorbitol/sorbitan mixture.
5. A dosage unit form as claimed in claim 1 in which the polyethylene glycol also contains glycerin, sorbitol or propylene glycol.
6. A dosage unit form as claimed in claim 5 in which the glycerin, sorbitol or propylene glycol is present in the polyethylene glycol in an amount of from 1 to 20% by weight.



INTERNATIONAL SEARCH REPORT

International Application No PCT.US84/00321

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC Int. Cl. ³ A01N 25/00 A23G/3/30 A61K 9/40		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	424/16, 19, 37 426/3, 5	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
Computer Search: Lexis, CAS Online		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category *	Citation of Document, ¹⁵ with Indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A	US, A, 2,847,346, Vaughan, 12 August 1958	1-6
A	US, A, 2,870,060, Bryan, 20 January 1959	1-6
A	US, A, 2,870,062, Stanley et al., 20 January 1959	1-6
Y	US, A, 2,889,252, Valentine et al., 02 June 1959	1-6
Y	US, A, 3,520,971, Benford, 21 July 1970	1-6
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Y	US, A, 3,779,942, Bolles, 18 December 1973	1-6
Y	US, A, 4,198,391, Grainger, 15 April 1980	1-6
A, P	US, A, 4,428,927, Elbert et al., 31 January 1984	1-6
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IV. CERTIFICATION		
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